DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 31, 2009 has been entered. New claims 39-42 have been added. Claims 3-4, 8, 15-18, 25 and 34-35 have been cancelled. Claims 1-2, 5-7, 9-14, 19-24, 26-33 and 36-42 are pending in this application and examined on the merits in this office action.

Maintained Rejection

35 U.S.C. 112, 2nd

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 9-11 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims recite, "...and derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin..." This phrase is unclear. It is unclear what modifications are encompassed within the derivatives and analogues of the

macromolecular principles, and what modifications are encompassed within derivatives or analogues conforming to structures derived from either human or animal origin.

Response to Applicant's Arguments

4. Applicant argues that "The Examiner's objections imply that the efficacy or success of the combined formulation depends closely on the exact sequence of the peptides/proteins being used according to the present invention…the mechanism by which the bile salts and acids operate according to the present invention is believed to involve the transient opening of large water channels such as tight junctions, through which active principles can diffuse." Applicant further argues that "the examples presented show that uptake can occur for different macromolecules which bear no resemblance to each other- insulin and salmon calcitonin. It is therefore reasonable to suppose that any other macromolecule would be taken up just as easily, regardless of its amino acid sequence in the case of peptides."

5. Applicant's arguments have been fully considered but have not been found persuasive. This rejection is based on the indefiniteness of what the derivatives and analogs of the macromolecular principles are. It is not clear what modifications are encompassed within the derivatives and analogs of these macromolecular principles. Regardless of what the mechanisms involved at the tight junction, it is unclear what modifications and derivatives the claims are referring to. For example, a derivative or analog of parathyroid hormone can be any sequence variance of this wildtype sequence, or any addition, deletion or substitution or any mutation to this sequence.

Therefore, there is vast number of derivatives and analogs of parathyroid that may be encompassed within the term. Furthermore, since the derivative or analogs may also be synthetic, it is unclear what modifications are encompassed within the derivatives or analogs conforming to structures derived from either human or animal origin. The specification does not define what derivatives and analogs and structures derived from either human or animal origin are. Therefore, the claim is indefinite.

35 U.S.C. 112, 1st

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 9-11 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the

genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to an active macromolecular principle chosen from insulin, calcitonin, growth hormone, parathyroid hormone, erythropoietin, GLP-1 and GCSF, and derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin. The generic statements derivatives and analogues thereof, either synthetic or from natural sources, conforming to structures derived from either human or animal origin do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 9-11 and 19-21 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds to make the variants or derivatives of the class of macromolecular polypeptides. It must not be forgotten that the MPEP states that if a peptide is described only by a functional

characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives, analogues and sequence variants of the polypeptides. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic or peptidomimetic or amino acid mimetic molecules that can form peptide bonds to form peptide-like molecules, and other synthetic small molecules that can function as peptide-like molecules.

The specification discloses that polypeptides and proteins such as insulin, calcitonin, human serum albumin, growth hormone…erythropoeitins and EPO mimetics, colony stimulating factors including GCSF and GMCSF…GLP-1…enzymes including histone deacetylase, superoxide dismutase…collagen, elastin or fibronectin…antibody molecules…proteins or peptides containing antigenic epitopes and fragments, and derivatives, conjugates and sequence variants of any of the above (see pp. 3-4 of specification). The working examples describes insulin as active macromolecular principle (see Examples 1, 6 and 8-9); calcitonin as active macromolecular principle

(see Example 7). The specification does not describe any of the derivatives, conjugates, sequence variants or analogues of the polypeptides described. Description of insulin and calcitonin is not sufficient to encompass numerous other proteins that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, human calcitonin has 93 amino acid residues (see GenBank Accession No. CAA26189). A derivative of calcitonin can have amino acid substitutions, deletions or additions and other modifications along the amino acid sequences. There are 20 naturally occurring amino acids, thus there are $93^{20} = 2.3 \times 10^{39}$ different possibilities. When non-natural amino acids (such as D-isomers, β-amino acids, γ-amino acids, ε-amino acids and modified amino acids) are factored into the equation, the numbers are innumerable. For a larger macromolecular protein such as growth hormone (GenBank Accession No. AAA49464) having 200 amino acids, there are $200^{20} = 1.05 \times 10^{46}$ different possibilities for naturally occurring amino acids alone. Therefore, the numbers of possibilities of derivatives, analogs or sequence variants of the polypeptides would increase according to the number of residues of that particular polypeptide. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals

appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

8. Applicant argues that "The Examiner's objections imply that the efficacy or success of the combined formulation depends closely on the exact sequence of the peptides/proteins being used according to the present invention...the mechanism by which the bile salts and acids operate according to the present invention is believed to involve the transient opening of large water channels such as tight junctions, through which active principles can diffuse." Applicant further argues that "the examples presented show that uptake can occur for different macromolecules which bear no resemblance to each other- insulin and salmon calcitonin. It is therefore reasonable to suppose that any other macromolecule would be taken up just as easily, regardless of its amino acid sequence in the case of peptides."

9. Applicant's arguments have been fully considered but have not been found persuasive. The working examples describe insulin and calcitonin as active macromolecular principle. As Applicant has indicated, these two wild type principles

have two different sequences, tertiary structures, isoelectric points and molecular weights. However, having these different genus modified to the derivatives and analogues having the same function could be innumerable. As described in the body of the rejection, the specification does not describe any of the derivatives, conjugates, sequence variants or analogues of the polypeptides described. Description of insulin and calcitonin is not sufficient to encompass numerous other proteins that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For example, human calcitonin has 93 amino acid residues (see GenBank Accession No. CAA26189). A derivative of calcitonin can have amino acid substitutions, deletions or additions and other modifications along the amino acid sequences. There are 20 naturally occurring amino acids, thus there are $93^{20} = 2.3 \times 10^{39}$ different possibilities. When non-natural amino acids (such as D-isomers, β-amino acids, γ-amino acids, ε-amino acids and modified amino acids) are factored into the equation, the numbers are innumerable. For a larger macromolecular protein such as growth hormone (GenBank Accession No. AAA49464) having 200 amino acids, there are $200^{20} = 1.05 \times 10^{46}$ different possibilities for naturally occurring amino acids alone. Additionally, for parathyroid hormone having 144 amino acid residues, this implies that there are $144^{20} = 8.37 \times 10^{22}$ different possibilities (GenBank Accession No. AAA72730). For any single, double or triple-stranded RNA, this also can have varying sequences, lengths, and characteristics. Therefore, the numbers of possibilities of derivatives, analogs or sequence variants of the polypeptides and RNA sequences would increase according to the number of residues of that

particular polypeptide or RNA sequence. Regardless of what the mechanisms involved at the tight junction, Applicant has not shown that the Applicant was in possession of all of the derivatives and analogs and those macromolecular principles that conform to structures derived from either or animal origin. Therefore, there is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

35 U.S.C. 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-2, 5-7, 9-14, 19-24, 26-33 and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over New (US Patent No. 5,853,748) in view of Desai (US Patent No. 5,206219) and Sonnenberg & Kotchen (Curr. Op. Neph. Hyperten., 1998, 7,

551-555). Please note that claims 19-24 were inadvertently omitted, but rejected in the body of the rejection below in the previous office action.

13. New teaches a pharmaceutical composition of (i) a biologically active proteinaceous material, oligonucleotide or analogue there of or polysaccharide; (ii) a bile acid or salt; and (iii) an agent having the ability to adjust the pH of the gut to a value of from 7.5 to 9 (see claim 1). New teaches specific example of macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4), meeting the limitation of claims 9-11 and 19-21. New teaches that sodium carbonate or bicarbonate can increase the solubility of the bile acids (see column 6, lines 4-7), and thus increase the permeability of bioactive through epithelial cells (see column 6, lines 4-19). New further teaches a composition with an enteric coating designed to prevent digestion in the stomach and to permit digestion in the small intestine (see column 7, lines 37-40), meeting the limitation of claims 31-35. New teaches a method of enhancing the absorption of the insulin across the intestinal wall in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition, meeting the limitation of claims 24, 26, 32 and 35. Further, the composition comprises less than 5% by weight of water (see table in example 4), meeting the limitations of claims 2 and 22. New teaches that the additive, sodium bicarbonate, is present at 8.3% by weight which is greater than 1% (table in Example 4). The ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in Example 4). New teaches that the quantity of bile acid contained in a single dose of the formulation will

vary depending on the particular bile acid chosen and the rate and extent to which that bile acid dissolves in the aqueous fluid contained in the intestine. For chenodeoxycholic acid, and most other bile acids, this is likely to be within range 10 mg to 1 g, preferably between 20 mg to 200 mg (most preferably 30 mg to 100 mg). For deoxycholic acid, the maximum will generally noat exceed 500 mg, in view of slightly greater activity (see column 3, lines 49-57), meeting the limitation of claims 39-40.

New teaches that the composition is in the form of a solution (see column 7, lines 5-55) or a solid (example 4), meeting the limitation of claims 6-7 and 23. The composition sensitizes the subject to insulin by increasing uptake (see example 4), meeting the limitation of claims 11 and 21. The non-conjugated bile acid is chenodeoxycholic acid, the acid form of chenodeoxycholate. New teaches that in general, bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions. New teaches that the buffering agent has the effect of buffering the compositions of the composition at a pH of about 7.5 or above, the solubilized bile salt will be present rather than the insoluble bile acid. A solubilized bile salt will be able to act on the epithelial cells when in solution, whereas this may not be possible in the solid acid form (see column 6, lines 6-14). Furthermore, New teaches that the higher the concentration of buffering agent, the more rapidly will a satisfactory pH be attained, resulting in more rapid dissolution of the bile acid or salt, resulting in a higher local concentration of the bile salt in solution, leading to greater efficacy in enhancing permeability to bioactive materials (see column 6, lines 14-19). The reference further teaches that the composition is dispersed in water

(see for example, claim 8), meeting the limitation of new claims 36-37. The difference between the reference and the instant claims is that the reference does not teach propyl gallate or butyl hydroxyl anisole (BHA) and further addition of insulin sensitizing agent.

14. However, Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations and antioxidants like butylated hydroxyanisole (BHA), butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (see column 5, lines 5-18). Typical antioxidant concentrations can be used which is usually a standard practice; these can be from 0.1% to 1.5% (w/w or w/v). Desai further teaches a dosage unit pharmaceutical composition, adapted for oral administration, containing as active proteinaceous ingredients erythropoietin, insulin growth hormones, calcitonin, GCSF, cyclosporine, vasopressin or its agonists and antagonists…interferons or interleukins (see column 2, lines 13-18, and Examples 1-4).

15. Furthermore, Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients (see page 552).

16. It would have been obvious to one of ordinary skill in the art to add in antioxidants or preservatives, such as butyl hydroxyl anisole (BHA) or propyl gallate, since these additives are commonly used for preserving the pharmaceutical formulation, and prevent degradation, to enhance the longer shelf life of the proteinaceous

ingredients. Furthermore, since New teaches the presence of sodium bicarbonate had beneficial effect by increasing the solubility of the bile acids to soluble bile salts and enhanced the permeability to bioactive materials (see New column 6, lines 4-7 and lines 17-19). Therefore, since New teaches the increased solubility of the bile acid or salt by sodium bicarbonate and teaches the pharmaceutical composition comprising an active macromolecule (insulin) and a non-conjugated bile acid or salt and sodium bicarbonate, it would have been obvious to add a well known antioxidant to preserve the pharmaceutical formulation. Since combination of sodium bicarbonate (additive) increased the solubility of the bile acid, then combination of a known antioxidant into the formulation would also have the same solubility. One of ordinary skill in the art would have been motivated to add in the antioxidants or preservatives to the pharmaceutical composition since these adjuvants would preserve the formulation, prevent degradation, and thus increase the shelf life of the pharmaceutical composition.

Further, it would have been obvious to one of ordinary skill in the art to maintain the pH of the intestinal fluid between pH 6.8 to 7.5, since New teaches that bile salts start to convert to its conjugate acid at pH of about 6.8 or below, and the acid form is insoluble in aqueous solution, and the buffering agent has the effect of buffering the compositions of the invention to a pH of about 7.5 or above, in which the solubilized bile salt will be present rather than the insoluble acid. One would be motivated to maintain the pH of the intestinal fluid not above pH 7.0, since New teaches that the bile salts begin to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions (see New column 6, lines 6-8). New additionally

teaches that the pH of the gut is between 5 to7 (see column 4, lines 17-19). A solubilized bile salt will be able to act on the epithelial cells when in solution. There is a reasonable expectation of success, since the New reference teaches enhanced permeability of the bioactive agents by solubilizing the bile acids using the sodium bicarbonate, thus addition of an antioxidant (that prevents the degradation of peptide or protein in the pharmaceutical formulation) would also have the same solubility. Further, maintaining the intestinal fluid between pH 6.8 and 7.0 would allow the bile salt to be in the soluble salt non-conjugated form to act on the epithelial cells when in solution in the intestinal fluid, which will lead to greater efficacy in enhancing permeability to bioactive materials, such as insulin and other protein drugs.

Additionally, it would have been obvious to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. One of the ordinary skilled in the art would have been motivated to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients. There would have been a reasonable expectation of success, since the FDA has approved the use of troglitazone in combination with insulin, and has been shown to work in clinical trials involving diabetic patients.

In regards to instant claim 8 that recites, "A composition according to claim 1 wherein, when the composition is introduced into the intestine, the additive (c) enhances

the solubility of the non-conjugated bile salt, the MPEP states the following: Furthermore, with respect to claim 8 which recites "wherein, when the composition is introduced into the intestine, the additive (c) enhances the solubility of the non-conjugated biloe salt" according to MPEP 2111.04: "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." Id. <". In the instant case, it is not deemed that the "wherein" clause limits the claim to particular structural features. Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

17. Applicant argues that "claims 1 and 26 have now been amended to require the presence of a minimum of 60 mg of the bile acid or salt for use according to the invention...the amount of acid that would now be required in order to reduce the pH of the relevant composition from 8-8.5 down to 6.8-7.5 is not significantly higher, to the extent that it really would be unfeasible to reduce the pH in the manner suggested by the Examiner." Applicant argues that "the claims are now directed to solid formulation." In the 132 Declaration, Dr. New argues that "in the first experiment, a total of 1.1 ml of HCl was required to bring the pH down by approximately 1.5 units, whereupon the solution precipitated at pH 6.70." Additionally, in the second experiment (using citric acid), precipitation occurred close to pH 6.7. Dr. New indicates that "8.4 mg of citric acid was required to bring the pH to neutrality...the experiments demonstrate that neither the presence of bicarbonate, nor citric acid, permit the chenodeoxycholate to be soluble at pHs found in the small intestine, since precipitation was noted in both cases at approximately 6.7."

18. Applicant's arguments have been fully considered, but have not been found persuasive.

The primary reference (New) teaches a pharmaceutical composition comprising an active macromolecular polypeptide (insulin), a non-conjugated bile acid or salt (in the range of 10 mgs to 1 g) and an additive (sodium bicarbonate). New teaches that the amount of bile acid will vary depending on the particular bile acid chosen and the rate and extent to which that bile acid dissolves in the aqueous fluid contained in the

intestine. The most preferred amount for chenodeoxycholic acid was from 30 mg to 100 mg (see column 3, lines 52-55). The addition of sodium bicarbonate increased the solubility of the bile salt, thereby increasing the permeability of the bioactive agents across the cell wall. Therefore, addition of a well known antioxidant (preservative) would have the same solubility. Additionally, the claim recites that "when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.0." This is the function of the solid pharmaceutical composition. The claims further recite, "wherein the additive is capable of allowing the non-conjugated bile acid or salt to remain in solution..." This implies that the function may or may not occur. Thus, since the combined arts teach all of the active components of the instant composition, this composition "is capable of allowing the non-conjugated bile acid or salt to remain in solution." Claim 1 does not recite that the pharmaceutical composition and the active agents must be in certain amounts or concentrations.

In regards to the 132 declaration, Applicant is reminded that claim 1 is drawn to a solid pharmaceutical composition. The primary reference (New) teaches a pharmaceutical composition comprising a macromolecular polypeptide (insulin), a non-conjugated bile acid or salt, and an additive (sodium bicarbonate) that increases the solubility of the non-conjugated bile acid, thus enhancing the permeability of the bioactive molecule. An addition of a well known antioxidant to the pharmaceutical composition that would preserve the formulation would have the same solubility, since the pharmaceutical composition having the sodium bicarbonate already increased the solubility of the bile acid. Since the pharmaceutical composition is in a solid form, it does

not matter that the formulation would precipitate out at pH 6.8. The New reference teaches that "bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions, it would have been obvious to one or ordinary skill in the art to maintain the pH of the intestinal fluid in between pH 6.8 to 7.5. New reference teaches that the pH of the gut is between 5 to 7, therefore, one would have been motivated to maintain the pH of about 7. Furthermore, one of ordinary skill in the art would have been motivated to combine the well known antioxidant to the pharmaceutical formulation, since the secondary reference (Desai) teaches that these adjuvants preserve the pharmaceutical formulation, thus increasing the shelf-life of the proteinaceous bioactive agents. Since sodium bicarbonate increases the solubility, and antioxidants are known to increase the shelf-life of the bioactive agents, one of ordinary skill in the art would have been motivated to use together, to achieve the optimal proteinaceous bioactive agent composition. Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations (see column 5, lines 6-7) and some of the oil soluble antioxidants listed are butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, propyl gallate, etc (see column 5, lines 16-18). The examples show different biologically active peptides (see column 2, lines 13-18), such as insulin and d-α-tocopherol (part of the oil soluble antioxidant) (see Example 1); erythropoietin and d-α-tocopherol (see Example 2); human growth hormone and d-α-tocopherol (see Example 3); calcitonin and d-α-tocopherol (see Example 4). Therefore, one of ordinary skill in the art would have been motivated to use any of the oil soluble antioxidants listed. Further, the components (a) and (b) may already be in a

solubilized form. There is no indication that (a) and (b) did not form a soluble formulation, and then the addition of (c) would form a solid composition, or after the addition of (c), the composition was solidified or purified.

New Objection

19. Claims 40 and 42 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 40 and 42 are dependent on claim 26, which recites, "A method of enhancing the absorption of an active macromolecular principle..." Claims 40 and 42 recite, "A composite/ composition of claim 26..." Since claim 26 recites a method and claims 40 and 42 recite a composite/ composition, claims 40 and 42 do not further limit claim 26.

20. Claim 40 is objected to for the following minor informality: Claim 40 is inconsistent with the claims 26 and 42. Claim 40 recites, "A composite according to claim 26..." Claim 26 recites, "A method of enhancing the absorption of an active macromolecular principle...in a solid pharmaceutical composition..." The "composite" should be corrected to "composition".

New Rejection

35 U.S.C. § 112, 1st

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

Claims 39-40 are drawn to a composition according to claim 1 (for claim 39) and according to claim 26 (for claim 40), containing at least 66 mg of the non-conjugated bile acid or salt.

Lack of Ipsis Verbis Support

23. The specification is void of any literal support for the "at least 66 mg or higher concentration of bile acid or salt" claimed. In the context of at least 66 mg, the word "at least" implies that there is 66 mg or greater of bile acid or salt added. The only amount disclosed in the instant specification is "66 mg chenodeoxycholic acid" at paragraphs [0059]-[0062] and 10 mg chenodeoxycholate diluted out to 150 μl volume (see paragraph [0056]). No range of "at least 66 mg to X mg" of bile acid or salt is disclosed in the instant application.

Lack of Implicit or Inherent Support

24. "While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for the claimed "at least 66 mg" of non-conjugated bile acid or salt. As explained supra, there is no support for any concept of "upper limit" of bile acid or salt or "a range" of bile acid or salt in the specification. At least 66 mg of bile acid or salt implies that there is an upper limit of bile acid or salt. However, only 10 mg of chenodeoxycholate and 66 mg of chenodeoxycholic acid are described in the specification and examples. Additionally, there are no examples that involve any amount greater than 66 mgs of bile acid or salt in the specification.

Conclusion

25. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Julie Ha/
Examiner, Art Unit 1654